

SOX10

Orthologs

Xenopus sox10 is expressed in developing neural crest, is induced by the FGF and Wnt signaling pathways, and colocalizes with *slug* and *sox9*. These three transcription factors appear to regulate one another during early neural crest development. Later in development *sox10* expression persists in trunk neural crest. Ectopic overexpression of *sox10* increases *slug* expression, and induces ectopic melanocyte precursors and melanocytes. Morpholino experiments showed that *sox10* inhibition results in loss of neural crest cell formation and that *sox10* is required for later development of pigment cells and ganglia. In addition, *sox10* is unable to induce ectopic melanoblasts during gastrulation, and together these data suggest **Xenopus sox10 functions early in neural crest development to specify cells to the pigment cell lineage** ([Aoki et al., 2003](#), [Honore et al., 2003](#)).

Cranial NC expression of SOX10 shows species variation: In *Xenopus*, chick, and human, *SOX10* is strongly expressed in cranial NC cells migrating into the branchial arches which gives rise to craniofacial mesoderm, while mice and zebrafish show no *Sox10* expression in these migrating cranial NC ([Aoki et al., 2003](#), [Bondurand et al., 1998](#)).

In the chick embryo, ectopic overexpression of SOX10 in the neural tube increases cells undergoing an epithelial to mesenchymal transition, and these cells express neural crest markers and migrate out of the neural tube. These SOX10-overexpressing cells are subsequently maintained in an undifferentiated state. These results suggest that **in the chick embryo, SOX10 acts to promote early neural crest migration, but downregulation of SOX10 levels are needed for later differentiation** ([McKeown et al., 2005](#)). These results correlate with previous in vitro mouse studies ([Kim et al., 2003](#)).

Zebrafish Sox10 is encoded by *colourless (cls)*. Analysis of *cls* mutants showed *sox10* is downregulated in pigment cell precursors, and also showed that in the absence of *sox10*, the neural crest cells that form non-ectomesenchymal derivatives (neurons, pigment cells, and glia) are not formed and die by apoptosis during development. Morpholino *sox10* experiments showed that *sox10* downregulation results in the absence of *nacre* and *spa* (*Kit* homolog) expression ([Dutton et al., 2001](#)).

Zebrafish *sox10* exhibits different, less complex downstream target regulation compared to murine *Sox10*. In the absence of *Sox10* (*cls* mutants), targeted *mitf* expression in neural crest can rescue pigmentation in zebrafish, suggesting that the sole function of *Sox10* in zebrafish pigment cells is activation of *mitf* ([Elworthy et al., 2003](#)). In contrast, *Mitf* expression in mouse melanoblasts that lack endogenous *Sox10* results in partial induction of genes necessary for pigmentation; *Dct*, *Pmel17*, and *Tyrp1* are induced, but *Tyr* is not ([Hou et al., 2006](#)). This demonstrates that **unlike zebrafish pigment cells, mouse melanocytes require both *Mitf* and *Sox10*, including a feedback loop governing *Tyr* expression, for full differentiation.**

Analysis of otic vesicle expression of zebrafish *sox10*, along with that of the related genes *sox9a* and *sox9b*, showed that strong *sox10* expression is maintained in otic epithelial cells, and that these 3 SOXE genes exhibit complex intra-regulation of each other. In *sox10* mutants, most otic cell types develop but are disorganized. In addition, single cell labeling indicated that only a small neural crest cell population migrates to the otic vesicle and these cells subsequently disappear. This suggests that **the auditory defects seen in mouse *Sox10* mutants and WS individuals may be the result of disruption of the strong *sox10* expression in the otic epithelium** (resulting in disorganized otic structures), rather than solely due to absence of melanocytes ([Dutton et al., 2009](#)).

In zebrafish, mutation of *disc1*, a gene associated with schizophrenia susceptibility which encodes a novel protein not associated with any known protein family, resulted in altered neural crest cell migration. This phenotype correlated with increased expression of *sox10* and *foxd3*, suggesting that

Disc1 normally functions to repress *sox10* and *foxd3* expression. This proposes a model in which Disc1 negatively regulates *sox10* and *foxd3*, thus tightly regulating the timing that allows neural crest cells to progress into later stages of differentiation ([Drerup et al., 2009](#)).

Analysis of the *SOX10* genomic region in chick identified two distinct enhancer regions located approximately 1kb downstream of *SOX10*. One, termed Sox10E1, regulates *SOX10* expression in later migrating vagal and trunk neural crest cells in chick. Interestingly, the other region, termed Sox10E2, regulates *SOX10* expression exclusively in chick early cranial neural crest, and a variety of assays showed that this region was directly bound and activated by SOX9, ETS1, and cMYB, at binding sites showing relatively high levels of cross-species conservation ([Betancur et al., 2010](#)). Further analyses of SOX10E2 regulation in the otic placode showed that while the same binding motifs within SOX10E2 are used in neural crest and otic placode, different SOX and ETS transcription family members are used in each tissue, with SOX9, ETS1, and cMYB in neural crest, and SOX8, PEA3, and cMYB in otic placode ([Betancur et al., 2011](#)).

Replacement of murine *Sox10* with the drosophila ortholog *Sox100B* showed that it was able to compensate for endogenous *Sox10* during early stages of neural crest development, as the early formation and migration of neural crest appeared normal in homozygous *Sox100B* embryos. **In contrast, homozygous *Sox100B* embryos died at birth, indicating that later development of specific neural crest-derived lineages were abnormal. Melanocyte development was most adversely affected, as *Sox100B* heterozygotes exhibited a white belly and head spots, and *Sox100B* homozygotes showed severely reduced numbers of melanoblasts.** The development of other *Sox10*-expressing lineages showed variable affects of homozygosity for *Sox100B*: Schwann cells and oligodendrocytes appeared fully rescued, while other neuronal lineages showed incomplete rescue ([Cossais et al., 2010](#)).

Embryonic pigment gene expression, including that of *SOX10*, was examined in two chicken pigment mutants, the hyperpigmented Silky Fowl and hypopigmented White Leghorn ([Li et al., 2010](#)).

Microarray analyses in zebrafish demonstrated that **during neural crest development, *sox10* expression is positively regulated by the zinc finger transcription factor *Prdm1a*.** This was supported by: the significant reduction of *sox10* expression in trunk neural crest of *prdm1a* mutants, the increased expression of *sox10* and appearance of ectopic neural crest cells in embryos overexpressing *prdm1a*, and the marked rescue of mutant phenotypes in *prdm1a* mutants by *sox10* mRNA injection. Direct vs. indirect regulation of *sox10* by *Prdm1a* was not determined ([Olesnicki et al., 2010](#)).

An 8268bp deletion along with a 10bp insertion occurring 14kb upstream of the chicken *Sox10* locus was shown to be the cause of the Dark brown (*DB*) plumage color, in which eumelanin is reduced and pheomelanin increased in distinct plumage pigmentation patterns. This region partially overlaps with the region homologous to the murine *Hry* deletion, including the evolutionarily conserved region *Sox10-MCS7* ([Antonellis et al., 2008](#)). However, in contrast to *Hry* mice, which show widespread neural crest defects, *DB* only affects melanocyte eumelanin levels, even in the homozygous state ([Gunnarsson et al., 2011](#)).

A neural crest specific enhancer that regulated *Sox10* expression during later stages of chick neural crest development was identified in a study that created expression constructs for persistent expression in neural crest. This 3571bp enhancer was located at -10,762 bp to -7192 bp upstream of the chicken *Sox10* locus, and was active during later stages of neural crest development ([Yokota et al., 2011](#)).